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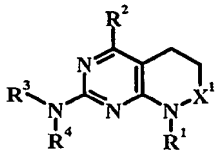
(54) Title: FUSED PYRIMIDINE DERIVATIVES WITH CRF ACTIVITY



(I)

(57) Abstract: This invention relates to compounds which are generally CRF-1 receptor antagonists and which are represented by Formula I wherein X^1 is $(CH_2)_n$, n is 0 to 2 and R^1, R^2, R^3 and R^4 are as defined in the specification; or individual isomers, racemic or non-racemic mixtures of isomers, or pharmaceutically acceptable salts thereof. The invention further relates to processes for preparing such compounds, to pharmaceutical compositions containing such compounds, and to methods for their use as therapeutic agents.

(*vii*) phenyl or heteroaryl said phenyl and heteroaryl optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, methylenedioxy C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, aminosulfonyl, monoalkylaminosulfonyl, dialkylaminosulfonyl, halogen, haloalkyl, cyano, nitro, and $-NR^aR^b$, where R^a and R^b are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{1-6} alkylcarbonyl,

(*viii*) naphthyl,

(*ix*) heteroaryl-C_{1-6}alkyl said heteroaryl-C_{1-6}alkyl optionally substituted with one to three substituents selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, aminosulfonyl, monoalkylaminosulfonyl, dialkylaminosulfonyl, halogen, haloalkyl, cyano, nitro, and $-NR^aR^b$, where R^a and R^b are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{1-6} alkylcarbonyl,

(*x*) 1,2-diphenylethyl,

(*xii*) C_{1-3} alkoxy-C_{1-6} alkyl, or,

(*xiii*) aryloxy-C_{1-6} alkyl said aryloxy group being optionally substituted with one to three substituents selected form the group consisting of C_{1-3} alkyl, C_{1-3} alkoxy and halogen;

R^2 is C_{1-6} alkyl or C_{1-3} haloalkyl;

R^3 is (*i*) hydrogen,

(*ii*) C_{1-6} alkyl optionally substituted with hydroxy, C_{1-3} alkoxy or C_{1-3} acyloxy,

(*iii*) C_{3-6} alkenyl,

(*iv*) C_{3-7} cycloalkyl,

(*v*) C_{3-7} cycloalkyl-C_{1-3} alkyl;

(*vi*) C_{3-7} cycloalkenyl,

(*vii*) C_{3-7} cycloalkenyl-C_{1-3} alkyl,

(*viii*) benzyl optionally substituted with one to three groups independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, aminosulfonyl, monoalkylaminosulfonyl, dialkylaminosulfonyl, halogen, haloalkyl, cyano, nitro, and $-NR^aR^b$, where R^a and R^b are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{1-6} alkylcarbonyl; and,

R^4 is aryl optionally substituted with one to three groups independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, aminosulfonyl, monoalkylaminosulfonyl, dialkylaminosulfonyl, halogen, haloalkyl, cyano, nitro, and $-NR^aR^b$, where R^a and R^b are each independently

Function and Potential for Therapeutic Intervention, Curr. Med. Chem.-Central Nervous System Agents 2001 1:63-97; D. A. Gutman *et al Corticotropin-releasing factor antagonists as novel psychotherapeutics, Drugs of the Future* 2000 25(9):923-31).

CRF antagonists are effective in the treatment of a wide range of stress-related illnesses, mood disorders such as depression, major depressive disorder, single episode depression, recurrent depression, child abuse induced depression, postpartum depression, dysthemia, bipolar disorder and cyclothymia; chronic fatigue syndrome; eating disorders such as obesity, anorexia and bulimia nervosa; generalized anxiety disorder; panic disorder; phobias; obsessive-compulsive disorder; post-traumatic stress disorder; pain perception such as fibromyalgia; headache; stress-induced gastrointestinal dysfunction such as irritable bowel syndrome (IBS), colonic hypersensitivity or spastic colon; hemorrhagic stress; ulcers; stress-induced psychotic episodes; inflammatory disorders such as rheumatoid arthritis and osteoarthritis; asthma; psoriasis; allergies; premature birth; hypertension; congestive heart failure; sleep disorders; neurodegenerative diseases such as Alzheimer's disease, senile dementia, Parkinson's disease and Huntington's disease; head or spinal cord trauma; ischemic neuronal damage; excitotoxic neuronal damage; epilepsy; stroke; psychosocial dwarfism; chemical dependencies and addictions; drug and alcohol withdrawal symptoms; stress-induced immune dysfunctions; immune suppression and stress-induced infections; cardiovascular or heart related diseases; fertility problems; and /or human immunodeficiency virus infections. Accordingly clinical data suggests that CRF receptor antagonists may represent novel antidepressants and/or anxiolytic drugs that may be useful in the treatment of the neuropsychiatric disorders manifesting hypersecretion of CRF.

5,8-Dihydro-6H-pyrido[2,3-d]pyrimidin-7-ones have been reported with a variety of pharmacological activities. WO 200259083 (J. L. Adams *et al.*) discloses 5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one compounds which are p38 kinase. WO2001055148 (R. J. Booth *et al.*) and WO 98 33798 (D. H. Boschelli *et al.*) report related compounds with cyclin-dependent kinase inhibitory activity. WO 98 01428 (C. Dominguez *et al.*) disclose amidinoindoles, amidinoazoles and analogs as inhibitors of Factor Xa and of thrombin.

While significant strides have been made toward achieving CRF regulation by administration of CRF receptor antagonists, there remains a need in the art for efficacious and selective small molecule CRF receptor antagonists. There is also a need for pharmaceutical compositions containing such CRF receptor antagonists, as well as

The term "optional" or "optionally" as used herein means that a subsequently described event or circumstance may, but need not, occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "optionally substituted" means that the moiety may be hydrogen or a substituent.

The term "alkyl" as used herein denotes an unbranched or branched chain, saturated, monovalent hydrocarbon residue containing 1 to 10 carbon atoms. The term "lower alkyl" denotes a straight or branched chain hydrocarbon residue containing 1 to 6 carbon atoms. "C_{1-10} alkyl" as used herein refers to an alkyl wherein alkyl is composed of 1 to 10 carbons. Examples of alkyl groups include, but are not limited to, lower alkyl groups include methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *i*-butyl, *t*-butyl or pentyl, isopentyl, neopentyl, hexyl, heptyl, and octyl and also include the alkyl groups specifically exemplified in the instant application.

The term "alkylene" as used herein denotes a divalent linear or branched saturated hydrocarbon radical, having from one to six carbons inclusive, unless otherwise indicated. Examples of alkylene radicals include, but are not limited to, methylene, ethylene, propylene, 2-methyl-propylene, butylene, and 2-ethylbutylene and also include the alkylene radicals specifically exemplified in the instant application.

The term "alkenyl" as used herein denotes an unsubstituted hydrocarbon chain radical having from 2 to 10 carbon atoms having one or two olefinic double bonds [preferably one olefinic double bond]. "C_{2-10} alkenyl" as used herein refers to an alkenyl composed of 2 to 10 carbons. Examples are vinyl, 1-propenyl, 2-propenyl (allyl) or 2-butenyl (crotyl) and also include the alkenyl radicals specifically exemplified in the instant application.

The term "bicyclic alkyl" or "tricyclyl akyl" as used herein denotes respectively two or three fused unsubstituted hydrocarbon cycles having from 4 to 12 carbon atoms. Examples include but are not limited to norbornane and adamantane.

The term "cycloalkyl" as used herein denotes a saturated carbocyclic ring containing 3 to 8 carbon atoms, i.e. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl as well as the cycloalkyl radicals specifically exemplified in the instant application. The term "C_{3-7} cycloalkyl" as used herein refers to an cycloalkyl composed of 3 to 7 carbons in the carbocyclic ring.

(alkyl)arylamino radicals also include those specifically exemplified in the instant application.

The term "alkoxy group" means an -O-alkyl group, wherein alkyl is as defined above such as methoxy, ethoxy, *n*-propyloxy, *i*-propyloxy, *n*-butyloxy, *i*-butyloxy, *t*-butyloxy, pentyloxy, hexyloxy, including their isomers as well as the alkoxy radicals specifically exemplified in the instant application. "Lower alkoxy" as used herein denotes an alkoxy group with a "lower alkyl" group as previously defined. "C_{1-10} alkoxy" as used herein refers to an-O-alkyl wherein alkyl is C_{1-10}.

The term "alkoxyalkyl" as used herein refers to the radical R'R"-, wherein R' is an alkoxy radical as defined herein, and R" is an alkylene radical as defined herein with the understanding that the attachment point of the alkoxyalkyl moiety will be on the alkylene radical. Examples are methoxymethyl, methoxyethyl, methoxypropyl, ethoxymethyl, ethoxyethyl, ethoxypropyl, propyloxypropyl, methoxybutyl, ethoxybutyl, propyloxybutyl, butyloxybutyl, *t*-butyloxybutyl, methoxypentyl, ethoxypentyl, propyloxypentyl including their isomers as well as the alkoxyalkyl radicals specifically exemplified in the instant application.

The terms "alkoxycarbonylalkyl" and "aryloxycarbonylalkyl"as used herein denotes the radical R'R" where R' is an alkoxycarbonyl or aryloxycarbonyl radical and R" is alkylene as defined herein and the attachment point of the aryl(alkoxy)carbonylalkyl radical will be on the alkylene radical. Examples of alkoxycarbonylalkyl radicals also include those specifically exemplified in the instant application.

The term "alkylthio" or "thioalkyl group" means an -S-alkyl group, wherein alkyl is as defined above such as methoxy, ethoxy, *n*-propyloxy, *i*-propyloxy, *n*-butyloxy, *i*-butyloxy, *t*-butyloxy, pentyloxy, hexyloxy, including their isomers. Examples of alkylthio groups also include those specifically exemplified in the instant application. "Lower alkylthio" or "lower thioalkyl" as used herein denotes an alkylthio group with a "lower alkyl" group as previously defined. "C_{1-10} alkylthio" as used herein refers to an-S-alkyl wherein alkyl is C_{1-10}.

The terms "alkylsulfonyl" and "arylsulfonyl" as used herein denotes a group of formula -$S(=O)_2R$ wherein R is alkyl or aryl respectively and alkyl and aryl are as defined herein. Examples of alkoxylsulfonyl radicals also include those specifically exemplified in the instant application.

The term "cycloalkenyl" as used herein denotes a unsaturated carbocyclic ring containing 4 to 8 carbon atoms, i.e. cyclobutenyl, cyclopentenyl, cyclohexenyl, cyclohepentyl or cyclooctenyl as well as the cycloalkenyl radicals specifically exemplified in the instant application. "C_{4-7} cycloalkenyl" as used herein refers to an cycloalkenyl composed of 4 to 7 carbons in the carbocyclic ring.

The term "cycloalkenylalkyl" as used herein refers to the radical R'R"-, wherein R' is a cycloalkenyl radical as defined herein, and R" is an alkylene radical as defined herein with the understanding that the attachment point of the cycloalkenylalkyl moiety will be on the alkylene radical. Examples of cycloalkylalkyl radicals include, but are not limited to, cyclopropylmethyl, cyclohexylmethyl, cyclopentylethyl and also include the cycloalkenylalkyl radicals specifically exemplified in the instant application. C_{3-7} cycloalkyl-C_{1-3} alkyl refers to the radical R'R" where R' is C_{3-7} cyclolalkyl and R" is C_{1-3} alkylene as defined herein.

The term "halogen" or "halo" as used herein means fluorine, chlorine, bromine, or iodine.

The term "haloalkyl" as used herein denotes an unbranched or branched chain alkyl group as defined above wherein 1, 2, 3 or more hydrogen atoms are substituted by a halogen. Examples are 1-fluoromethyl, 1-chloromethyl, 1-bromomethyl, 1-iodomethyl, trifluoromethyl, trichloromethyl, tribromomethyl, triiodomethyl, 1-fluoroethyl, 1-chloroethyl, 1-bromoethyl, 1-iodoethyl, 2-fluoroethyl, 2-chloroethyl, 2-bromoethyl, 2-iodoethyl, 2,2-dichloroethyl, 3-bromopropyl or 2,2,2-trifluoroethyl and also include the haloalkyl radicals specifically exemplified in the instant application.

The term "heteroaryl" or "heteroaromatic" as used herein means a monocyclic or bicyclic radical of 5 to 12 ring atoms having at least one aromatic ring containing four to eight atoms per ring, incorporating one or more N, O, or S heteroatoms, the remaining ring atoms being carbon, with the understanding that the attachment point of the heteroaryl radical will be on an aromatic ring. As well known to those skilled in the art, heteroaryl rings have less aromatic character than their all-carbon counter parts. Thus, for the purposes of the invention, a heteroaryl group need only have some degree of aromatic character. Examples of heteroaryl moieties include monocyclic aromatic heterocycles having 5 to 6 ring atoms and 1 to 3 heteroatoms include, but is not limited to, pyridinyl, pyrimidinyl, pyrazinyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolinyl, thiadiazolinyl and oxadiazolinyl, as well as the heteroaryl moieties specifically exemplified in the instant application, which can optionally be

The terms "chloroalkylene" as used herein denotes the radical R'R" where R' is an chlorine radical and R" is alkylene as defined herein and the attachment point of the chloroalkylene radical will be on the alkylene radical. Examples of chloroalkylene radicals include those specifically exemplified in the instant application.

Also encompassed by the instant invention are compounds of formula I wherein,
X^1 is $(CH_2)_n$;
n is 0 to 2;
R^1 is (*i*) C_{1-10} alkyl optionally substituted with a substituent selected from the group consisting of amino, C_{1-3} alkylamino, C_{1-3} dialkylamino, (C_{1-3} alkyl)arylamino and phenyl, said phenyl optionally substituted with *(a)* one to three substituents independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, aminosulfonyl, monoalkylaminosulfonyl, dialkylaminosulfonyl, halogen, haloalkyl, cyano, nitro, and $-NR^aR^b$, where R^a and R^b are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{1-6} alkylcarbonyl,
(*ii*) C_{3-7} cycloalkyl optionally substituted with C_{1-3} alkyl,
(*iii*) C_{3-7} cycloalkyl-C_{1-3} alkyl,
(*iv*) benzofused-C_{5-7} cycloalkyl,
(*v*) phenyl or heteroaryl said phenyl and heteroaryl optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, aminosulfonyl, monoalkylaminosulfonyl, dialkylaminosulfonyl, halogen, haloalkyl, cyano, nitro, and $-NR^aR^b$, where R^a and R^b are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{1-6} alkylcarbonyl,
(*vi*) heteroaryl-C_{1-6}alkyl said heteroaryl-C_{1-6}alkyl optionally substituted with one to three substituents selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, aminosulfonyl, monoalkylaminosulfonyl, dialkylaminosulfonyl, halogen, haloalkyl, cyano, nitro, and $-NR^aR^b$, where R^a and R^b are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{1-6} alkylcarbonyl,
(*vii*) 1,2-diphenylethyl,
(*viii*) C_{1-3} alkoxy-C_{1-6} alkyl, or,
(*ix*) aryloxy-C_{1-6} alkyl said aryloxy group being optionally substituted with one to three substituents selected form the group consisting of C_{1-3} alkyl, C_{1-3} alkoxy and halogen;
R^2 is C_{1-6} alkyl or C_{1-3} haloalkyl;

alkyl, (*iii*) C_{3-7} cycloalkyl-C_{1-3} alkyl, or, (*iv*) benzyl optionally substituted with C_{1-3} alkyl, C_{1-3} alkoxy or halogen; R^4 is optionally substituted phenyl.

In another embodiment of the present invention there is provided a compound according to formula I wherein X^1 is $(CH_2)_n$; n is 0; R^1 is (*i*) C_{1-10} branched or unbranched alkyl, (*ii*) C_{1-10} alkyl substituted with a phenyl said phenyl optionally substituted, or (*iii*) heteroaryl-C_{1-6} alkyl wherein said heteroaryl is 2-thienyl, 2-furanyl or 3-indolinyl each of said heteroaryl being optionally substituted; R^2 is C_{1-6} alkyl or C_{1-3} haloalkyl; R^3 is (*i*) hydrogen, (*ii*) C_{1-6} alkyl, (*iii*) C_{3-7} cycloalkyl-C_{1-3} alkyl, or, (*iv*) benzyl optionally substituted with C_{1-3} alkyl, C_{1-3} alkoxy or halogen; R^4 is optionally substituted phenyl.

In another embodiment of the present invention there is provided a compound according to formula I wherein X^1 is $(CH_2)_n$; n is 0; R^1 is (*i*) C_{1-10} branched or unbranched alkyl, (*ii*) C_{1-10} alkyl substituted with a phenyl said phenyl optionally substituted, or (*iii*) heteroaryl- C_{1-6} alkyl wherein said heteroaryl is 2-thienyl, 2-furanyl or 3-indolinyl each of said heteroaryl being optionally substituted; R^2 is C_{1-6} alkyl or C_{1-3} haloalkyl; R^3 is (*i*) hydrogen, (*ii*) C_{1-6} alkyl, (*iii*) C_{3-7} cycloalkyl-C_{1-3} alkyl, or, (*iv*) benzyl optionally substituted with C_{1-3} alkyl, C_{1-3} alkoxy or halogen; R^4 is 2,4-disubstituted- or 2,4,6-trisubstituted-phenyl.

In another embodiment of the present invention there is provided a compound according to formula I wherein X^1 is $(CH_2)_n$, n is 0, R^2 is CH_3, R^3 is CH_2CH_3 and R^4 is 2,4-disubstituted- or 2,4,6-trisubstituted-phenyl. Preferred compounds for this embodiment may be selected from the group consisting of

Ethyl-[7-(1-ethyl-propyl)-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine,

(7-Cyclopropyl-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl)-ethyl-(2,4,6-trimethyl-phenyl)-amine,

(7-Cyclohexylmethyl-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl)-ethyl-(2,4,6-trimethyl-phenyl)-amine,

Ethyl-[4-methyl-7-(1,2,3,4-tetrahydro-naphthalen-1-yl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine,

Ethyl-[4-methyl-7-(1-methyl-3-phenyl-propyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine,

(7-Benzyl-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl)-ethyl-(2,4,6-trimethyl-phenyl)-amine,

Ethyl-[7-(3-fluoro-benzyl)-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine,

[7-(3,4-Dimethoxy-benzyl)-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-ethyl-(2,4,6-trimethyl-phenyl)-amine,

Ethyl-(4-methyl-7-phenethyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl)-(2,4,6-trimethyl-phenyl)-amine,

(7-Allyl-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl)-ethyl-(2,4,6-trimethyl-phenyl)-amine,

Ethyl-(4-methyl-7-propyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl)-(2,4,6-trimethyl-phenyl)-amine,

Ethyl-(4-methyl-7-pentyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl)-(2,4,6-trimethyl-phenyl)-amine,

Ethyl-[7-(3-imidazol-1-yl-propyl)-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine,

[7-(2-Cyclohex-1-enyl-ethyl)-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-ethyl-(2,4,6-trimethyl-phenyl)-amine,

3-{2-[Ethyl-(2,4,6-trimethyl-phenyl)-amino]-4-methyl-5,6-dihydro-pyrrolo[2,3-d]pyrimidin-7-yl}-propionitrile,

(7-Cyclopropylmethyl-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl)-ethyl-(2,4,6-trimethyl-phenyl)-amine,

Ethyl-[4-methyl-7-(1-phenyl-propyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine,

Ethyl-{7-[1-(4-fluoro-phenyl)-ethyl]-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl}-(2,4,6-trimethyl-phenyl)-amine,

Cyclopentyl-[4-methyl-7-(1-propyl-butyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine,

Acetic acid 4-[[4-methyl-7-(1-propyl-butyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amino]-butyl ester,

Benzyl-[4-methyl-7-(1-propyl-butyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine,

Cyclopropylmethyl-[4-methyl-7-(1-propyl-butyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine, and

Allyl-[4-methyl-7-(1-propyl-butyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine as well as their acid addition salt with trifluoro-acetic acid.

In another embodiment of the present invention there is provided a compound according to formula I wherein X^1 is $(CH_2)_n$; n is 1; R^1 is (*i*) C_{1-10} branched or unbranched alkyl, (*ii*) optionally substituted heteroaryl-C_{1-6}alkyl, said heteroaryl optionally substituted with a substituent selected from the group consisting of C_{1-3} alkyl, C_{1-3} alkoxy and halogen, (*iii*) optionally substituted phenyl or heteroaryl said phenyl or heteroaryl optionally substituted with a substituent selected from the group consisting of C_{1-3} alkyl, C_{1-3} alkoxy and halogen, or (*iv*) C_{1-3} alkyl substituted with a phenyl said phenyl optionally substituted with a substituent selected from the group consisting of C_{1-3} alkyl, C_{1-3} alkoxy and halogen; R^2 is C_{1-6} alkyl or C_{1-3} haloalkyl; R^3 is (*i*) hydrogen, (*ii*) C_{1-6} alkyl, (*iii*) C_{3-7} cycloalkyl-C_{1-3} alkyl, or, (*iv*) benzyl optionally substituted with C_{1-3} alkyl, C_{1-3} alkoxy or halogen; R^4 is optionally substituted phenyl.

In another embodiment of the present invention there is provided a compound according to formula I wherein X^1 is $(CH_2)_n$; n is 1; R^1 is (*i*) C_{1-10} branched or unbranched alkyl, (*ii*) optionally substituted heteroaryl-C_{1-6}alkyl, said heteroaryl optionally substituted with a substituent selected from the group consisting of C_{1-3} alkyl, C_{1-3} alkoxy and halogen, (*iii*) optionally substituted phenyl or heteroaryl said phenyl or heteroaryl optionally substituted with a substituent selected from the group consisting of C_{1-3} alkyl, C_{1-3} alkoxy and halogen, or (*iv*) C_{1-3} alkyl substituted with a phenyl said phenyl optionally substituted with a substituent selected from the group consisting of C_{1-3} alkyl, C_{1-3} alkoxy and halogen; R^2 is C_{1-6} alkyl or C_{1-3} haloalkyl; R^3 is (*i*) hydrogen, (*ii*) C_{1-6}

optionally substituted with a substituent selected from the group consisting of C_{1-3} alkyl, C_{1-3} alkoxy and halogen; R^2 is C_{1-6} alkyl or C_{1-3} haloalkyl; R^3 is (*i*) hydrogen, (*ii*) C_{1-6} alkyl, (*iii*) C_{3-7} cycloalkyl-C_{1-3} alkyl, or, (*iv*) benzyl optionally substituted with C_{1-3} alkyl, C_{1-3} alkoxy or halogen; R^4 is 2,4-disubstituted- or 2,4,6-trisubstituted-phenyl.

In another embodiment of the present invention there is provided a compound according to formula I wherein A compound according to claim 15 wherein X_1 is $(CH_2)_n$, n is 2, R^2 is CH_3, R^3 is CH_2CH_3 and R^4 is 2,4,6-trisubstituted-phenyl. Preferred compounds for this embodiment may be selected from the group consisting of

(9-Cyclohexylmethyl-4-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl)-ethyl-(2,4,6-trimethyl-phenyl)-amine,

Ethyl-(9-furan-2-ylmethyl-4-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl)-(2,4,6-trimethyl-phenyl)-amine,

Ethyl-(9-indan-1-yl-4-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl)-(2,4,6-trimethyl-phenyl)-amine,

Ethyl-(4-methyl-9-thiophen-2-ylmethyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl)-(2,4,6-trimethyl-phenyl)-amine,

Ethyl-(4-methyl-9-pyridin-3-ylmethyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl)-(2,4,6-trimethyl-phenyl)-amine,

[9-(1,2-Diphenyl-ethyl)-4-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl]-ethyl-(2,4,6-trimethyl-phenyl)-amine,

Ethyl-[9-(2-methoxy-1-methyl-ethyl)-4-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl]-(2,4,6-trimethyl-phenyl)-amine,

Ethyl-[4-methyl-9-(1-methyl-3-phenyl-propyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl]-(2,4,6-trimethyl-phenyl)-amine,

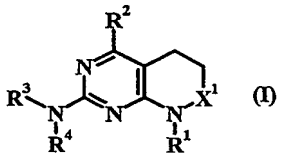
Ethyl-[9-(1-ethyl-propyl)-4-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl]-(2,4,6-trimethyl-phenyl)-amine,

(9-Benzyl-4-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl)-ethyl-(2,4,6-trimethyl-phenyl)-amine,

[9-(2,4-Dimethyl-benzyl)-4-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl]-ethyl-(2,4,6-trimethyl-phenyl)-amine, and

(4-Methyl-9-thiophen-2-ylmethyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl)-(2,4,6-trimethyl-phenyl)-amine, as well as their acid addition salt with trifluoro-acetic acid.

In another embodiment of the present invention there is provided the use of a compound of the following general formula I:



(I)

wherein

X^1 is C=O;

R^1 is (*i*) C_{1-10} alkyl or C_{2-10} alkenyl optionally substituted with a substituent selected from the group consisting of hydroxy, cyano, amino, C_{1-3} alkylamino, C_{1-3} dialkylamino, (C_{1-3} alkyl)arylamino and phenyl, said phenyl optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, aminosulfonyl, monoalkylaminosulfonyl, dialkylaminosulfonyl, halogen, haloalkyl, cyano, nitro, and $-NR^aR^b$, where R^a and R^b are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{1-6} alkylcarbonyl,

(*ii*) C_{3-7} cycloalkyl optionally substituted with C_{1-3} alkyl or hydroxy,

(*iii*) C_{3-7} cycloalkyl-C_{1-3} alkyl or C_{3-7} cycloalkenyl-C_{1-3} alkyl (example 49),

(*iv*) C_{4-12} bicyclic or tricyclic alkyl,

(*v*) C_{3-7} heterocycloalkyl or C_{3-7} heterocycloalkyl-C_{1-3} alkyl, optionally substituted with C_{1-3} alkyl, phenyl or phenyl-C_{1-6} alkyl or a CH_2 in the heterocyclic moiety can be replaced by a C=O,

(*vi*) benzofused-C_{5-7} cycloalkyl,

(*vii*) phenyl or heteroaryl said phenyl and heteroaryl optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, methylenedioxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, aminosulfonyl, monoalkylaminosulfonyl, dialkylaminosulfonyl, halogen, haloalkyl, cyano, nitro, and $-NR^aR^b$, where R^a and R^b are each

Preferred compounds for this embodiment may be selected from the group consisting of

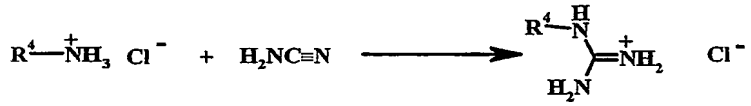
2-(2-Bromo-4-isopropyl-phenylamino)-8-(1-ethyl-propyl)-4-methyl-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one,

2-(2-Bromo-4-isopropyl-phenylamino)-4-methyl-8-(1-propyl-butyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one,

2-[(2-Bromo-4-isopropyl-phenyl)-ethyl-amino]-4-methyl-8-(1-propyl-butyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one, as well as their salt with hydrochloric acid.

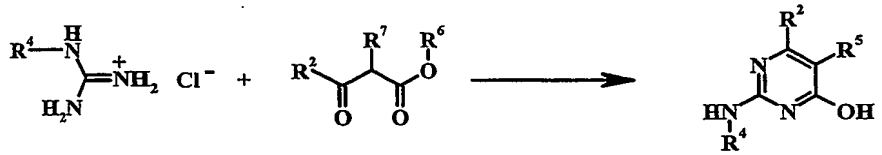
The compounds of the present invention of formula I wherein R^3 is hydrogen and X^1, R^1, R^2, R^4 and n are as defined hereinabove may be prepared according to a process comprising the steps of:

(*i*) contacting an aryl amine hydrochloride XXII wherein R^4 is as defined above with cyanamid to afford an aryl guanidinium hydrochloride XXIII;



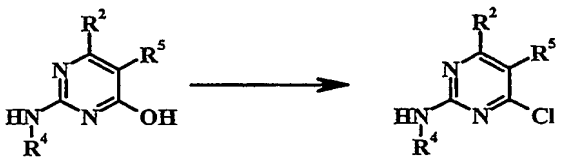
XXII XXIII

(*ii*) contacting said guanidine hydrochloride XXIII with a α-substituted β-keto ester XXIV wherein R^2 is C_{1-6} alkyl and R^6 is C_{1-6} alkyl and R^7 is alkoxycarbonylalkyl or R^6 and R^7 together are $(CH_2)_o$ and o is 2 to 4 in the presence of base to afford the pyrimidine XXV wherein R^5 is alkoxycarbonylalkyl or $(CH_2)_o$-OH;



XXIII XXIV XXV

(*iii*) contacting said pyrimidine with a chlorinating agent sufficiently reactive to convert XXV to the corresponding chloropyrimidine XXVI and to convert a hydroxyalkylene side chain present at R^5 to the corresponding chloroalkylene substituent;



XXV XXVI

COMPOUNDS AND PREPARATION

Compounds of the present invention can be made by a variety of methods depicted in the illustrative synthetic reaction schemes shown and described below. The starting materials and reagents used in preparing these compounds generally are either available from commercial suppliers, such as Aldrich Chemical Co., or are prepared by methods known to those skilled in the art following procedures set forth in references such as *Fieser and Fieser's Reagents for Organic Synthesis*; Wiley & Sons: New York, Volumes 1-21; R. C. LaRock, *Comprehensive Organic Transformations*, 2nd edition Wiley-VCH, New York 1999; *Comprehensive Organic Synthesis*, B. Trost and I. Fleming (Eds.) vol. 1-9 Pergamon, Oxford, 1991; *Comprehensive Heterocyclic Chemistry*, A. R. Katritzky and C. W. Rees (Eds) Pergamon, Oxford 1984, vol. 1-9; *Comprehensive Heterocyclic Chemistry II*, A. R. Katritzky and C. W. Rees (Eds) Pergamon, Oxford 1996, vol. 1-11; and *Organic Reactions*, Wiley & Sons: New York, 1991, Volumes 1-40. The following synthetic reaction schemes are merely illustrative of some methods by which the compounds of the present invention can be synthesized, and various modifications to these synthetic reaction schemes can be made and will be suggested to one skilled in the art having referred to the disclosure contained in this Application.

The starting materials and the intermediates of the synthetic reaction schemes can be isolated and purified if desired using conventional techniques, including but not limited to, filtration, distillation, crystallization, chromatography, and the like. Such materials can be characterized using conventional means, including physical constants and spectral data.

Unless specified to the contrary, the reactions described herein preferably are conducted under an inert atmosphere at atmospheric pressure at a reaction temperature range of from about -78 °C to about 150 °C, more preferably from about 0°C to about 125 °C, and most preferably and conveniently at about room (or ambient) temperature, e.g., about 20 °C.

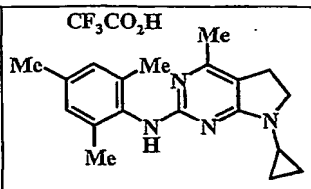
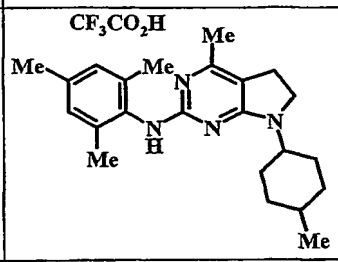
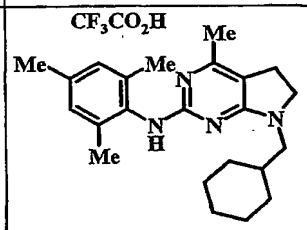
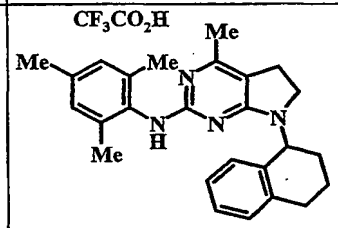
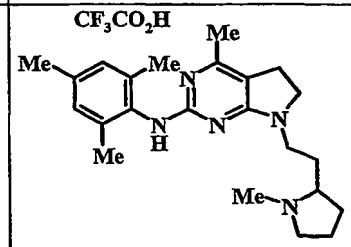
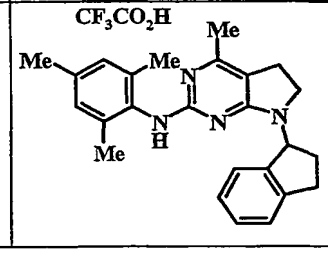
Some compounds in following schemes are depicted with generalized substituents; however, one skilled in the art will immediately appreciate that the nature of the R groups can varied to afford the various compounds contemplated in this invention. Moreover, the reaction conditions are exemplary and alternative conditions are well

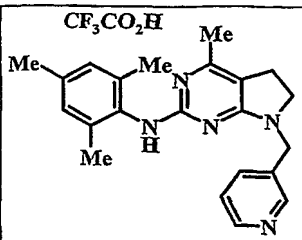
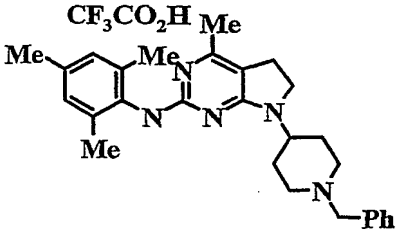
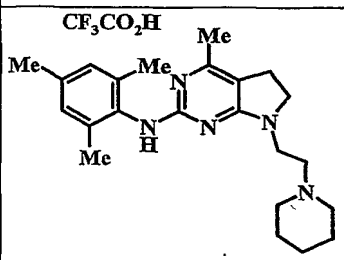
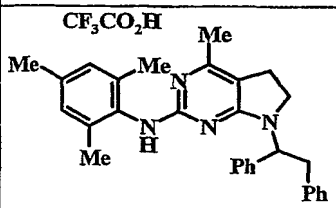
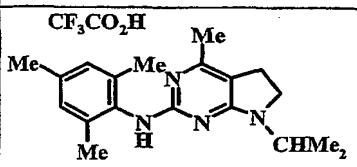
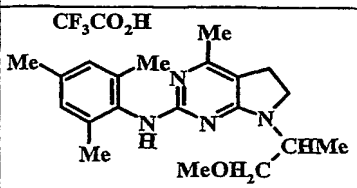
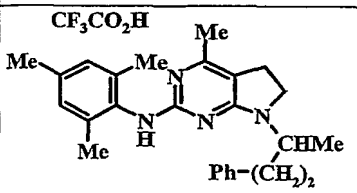
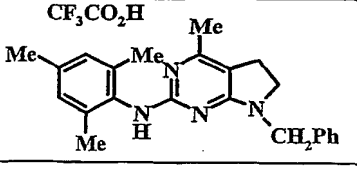
atom fragments. One fragment is a β-dicarbonyl compound. The carbonyls may be composed of ketones, aldehydes, carboxylic acid derivatives or nitriles. The second three atom segment is amidine which can be replaced by a urea, thiourea or guanidine. The range of equivalents capable of undergoing this reaction affords significant flexibility in the preparation of substituted pyrimidines. (D. J. Brown *Pyrimidines and their benzo Derivatives* in *Comprehensive Heterocyclic Chemistry,* A. J. Boulton and A. McKillop (ed) vol. 3 part 2b, chap. 2.13, Pergamon Press, Oxford 1984 pp. 57-157; D. J. Brown, *The Pyrimidines, Supplement II* in *The Chemistry of Heterocyclic Compounds*, A. Weissberger and E. C. Taylor (ed), Wiley Interscience, New York 1985, pp. 21-62)

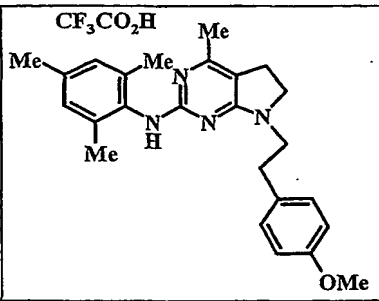
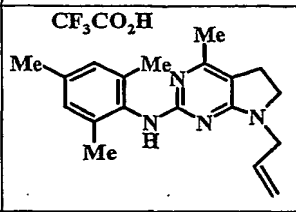
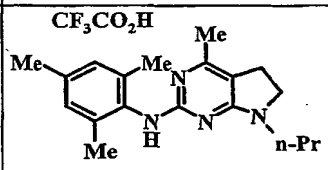
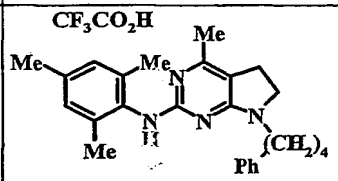
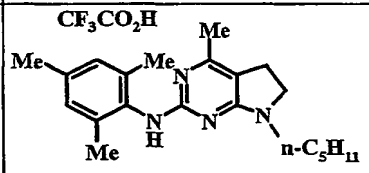
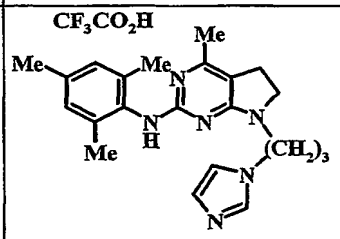
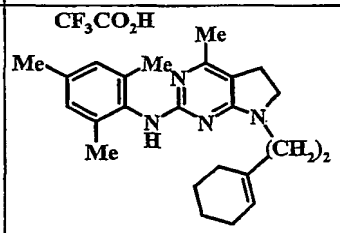
In the present case the 2 arylamino-substituted pyrimidines can be directly prepared by utilization of an aryl guanidine in the cyclization step. Aryl guanidines are readily prepared from aryl amines (I. A. Cliffe *Functional Groups Containing an Iminocarbonyl Group and Any Element Other than A Halogen or Chalogen* in *Comprehensive Functional Group Transformations*, Vol 6, T. L. Gilchrist (ed) Pergamon Press, Oxford, 1995, pp. 640-42) In step (*i*) an appropriately substituted aryl amine is converted to the corresponding guanidinium hydrochloride salt by condensation with cyanamid.

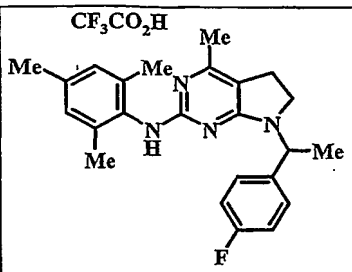
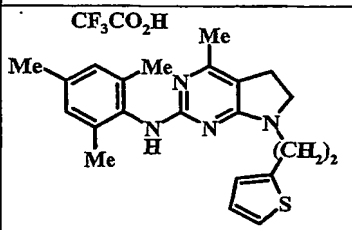
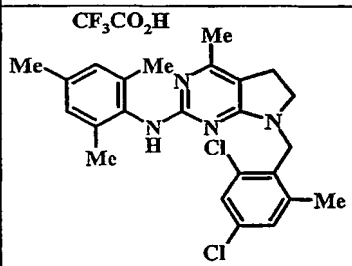
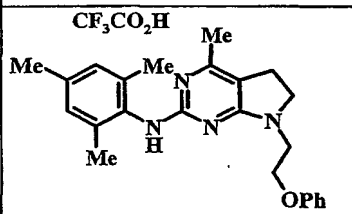
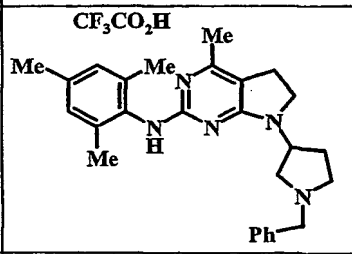
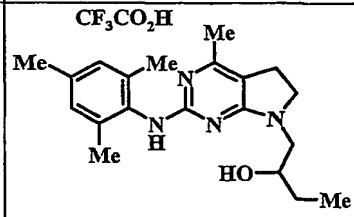
Step (b) exemplifies the Principal pyrimidine synthesis wherein a 2-arylaminopyrimidine is prepared by cyclization of the guanidine and 2-acetylbutyrolactone which introduces the desired 2-arylamino and 4-methyl substituents onto the pyrimidine ring in addition to the hydroxy ethyl moiety and the 6-hydroxy group which ultimately is cyclized to produce the fused pyrrolidine. One skilled in the art will readily appreciate that 2-acetylbutyrolactone formally is simply a 2-substituted acetoacetic acid derivative and the pyrimidine synthesis can be accomplished with variety of side chains which can alter the sized and substitution on the heterocyclic ring fused to the pyrimidine.

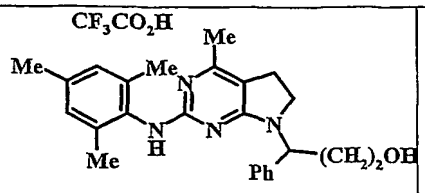
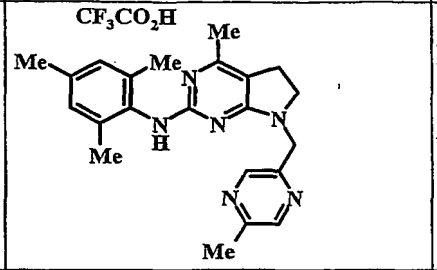
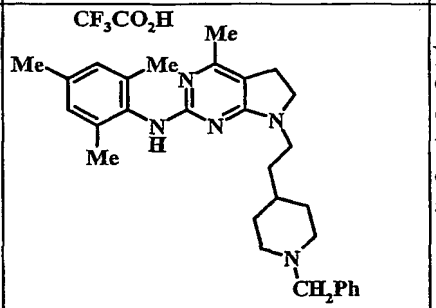
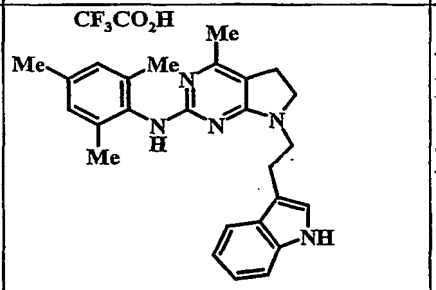
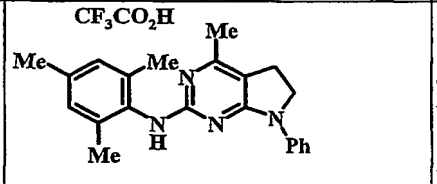
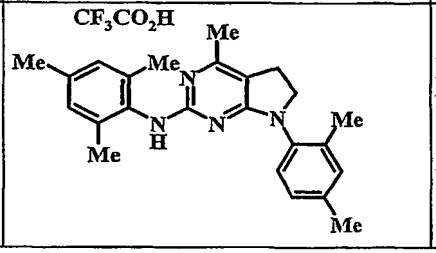
Hydroxy pyrimidines can be converted to halopyrimidines by treating the pyrimidinone with a phosphoryl halide, a phosphorus pentahalide, a phosphorus trihalide or mixtures thereof. Tertiary amine bases are sometimes used as catalysts for the halogenation. The halogenation reaction can be run in the presence of a variety of functional groups without interference (Brown *Comprehensive Heterocyclic Chemistry, supra* p139-140). In step (b) two chlorinations are carried out by sequential treatment of the diol VI with (*a*) thionyl chloride at room temperature which converts the hydroxyethyl side chain to the corresponding chloroethyl side chain and (*b*) phosphorus oxychloride at reflux which

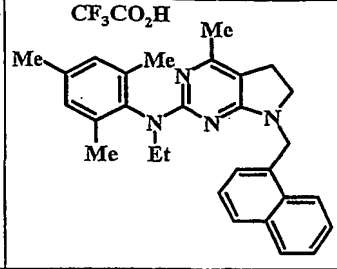
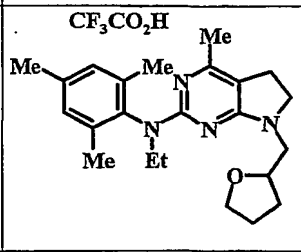
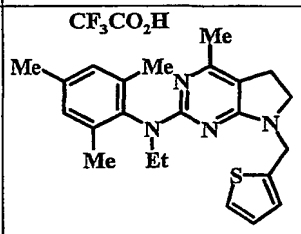
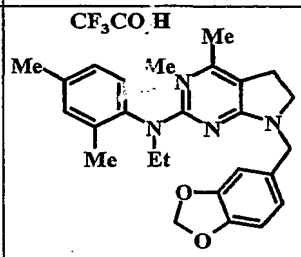
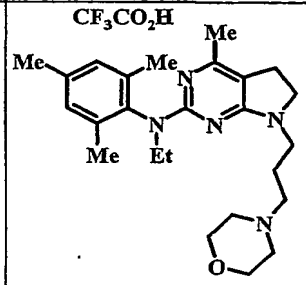
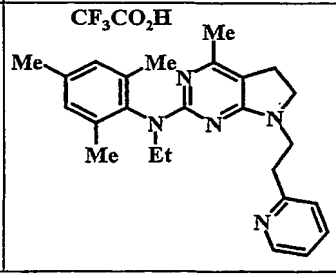
3		(7-Cyclopropyl-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl)-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		309.4 309
4		[4-Methyl-7-(4-methyl-cyclohexyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		365.5 365
5		(7-Cyclohexylmethyl-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl)-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		365.5 365
6		[4-Methyl-7-(1,2,3,4-tetrahydro-naphthalen-1-yl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		399.6 399
7		{4-Methyl-7-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl}-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		380.5 380
8		(7-Indan-1-yl-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl)-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		385.5 385

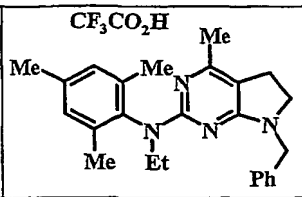
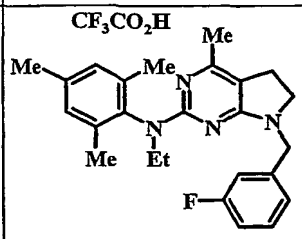
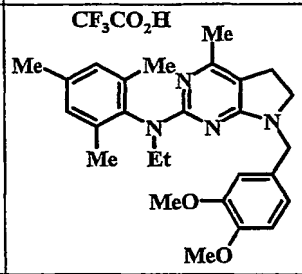
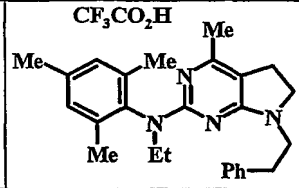
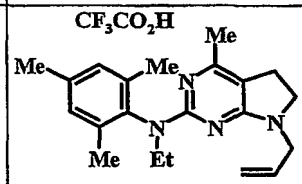
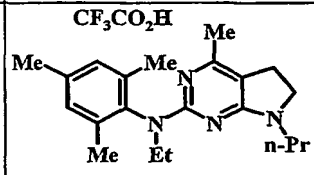
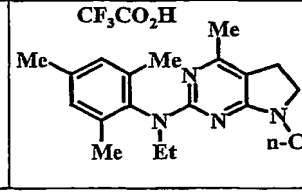
15		(4-Methyl-7-pyridin-3-ylmethyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl)-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		360.5 360
16		[7-(1-Benzyl-piperidin-4-yl)-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		442.6 442
17		[4-Methyl-7-(2-piperidin-1-yl-ethyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		380.5 380
18		[7-(1,2-Diphenyl-ethyl)-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		449.6 449
19		(7-Isopropyl-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl)-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		311.4 311
20		[7-(2-Methoxy-1-methyl-ethyl)-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		341.5 341
21		[4-Methyl-7-(1-methyl-3-phenyl-propyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		401.6 401
22		(7-Benzyl-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl)-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic		359.5 359

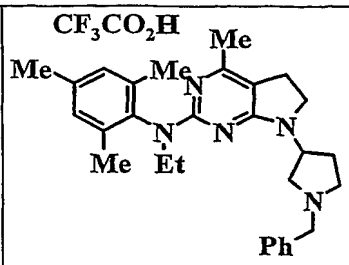
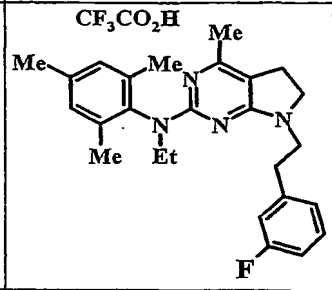
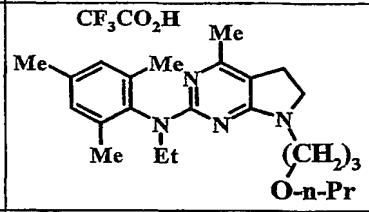
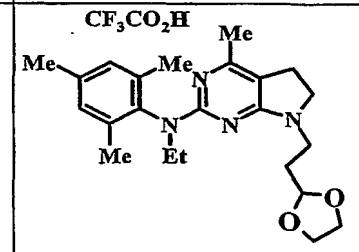
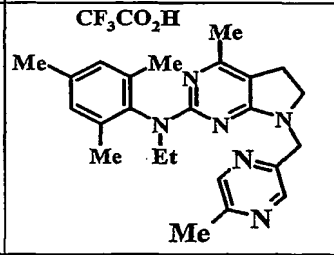
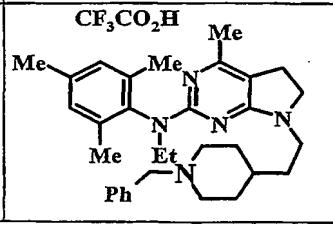
29		{7-[2-(4-Methoxy-phenyl)-ethyl]-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl}-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		403.5 403
30		(7-Allyl-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl)-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		309.4 309
31		(4-Methyl-7-propyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl)-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		311.4 311
32		[4-Methyl-7-(4-phenyl-butyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		401.6 401
33		(4-Methyl-7-pentyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl)-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		339.5 339
34		[7-(3-Imidazol-1-yl-propyl)-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		377.5 377
35		[7-(2-Cyclohex-1-enyl-ethyl)-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		377.5 377

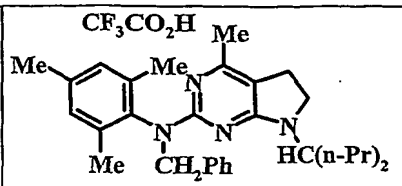
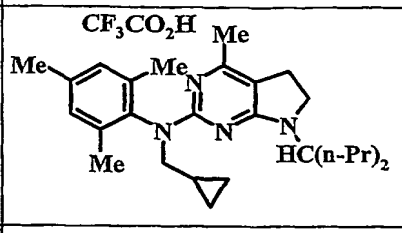
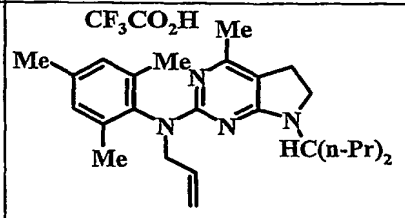
43		{7-[1-(4-Fluoro-phenyl)-ethyl]-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl}-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		391.5 391
44		[4-Methyl-7-(2-thiophen-2-yl-ethyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		379.5 379
45		[7-(2,4-Dichloro-6-methyl-benzyl)-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		441.4 441
46		[4-Methyl-7-(2-phenoxy-ethyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		389.5 389
47		[7-(1-Benzyl-pyrrolidin-3-yl)-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		428.6 428
48		1-[4-Methyl-2-(2,4,6-trimethyl-phenylamino)-5,6-dihydro-pyrrolo[2,3-d]pyrimidin-7-yl]-butan-2-ol; compound with trifluoro-acetic acid		341.5 341

56		3-[4-Methyl-2-(2,4,6-trimethyl-phenylamino)-5,6-dihydro-pyrrolo[2,3-d]pyrimidin-7-yl]-3-phenyl-propan-1-ol; compound with trifluoro-acetic acid		403.5 403
57		[4-Methyl-7-(5-methyl-pyrazin-2-ylmethyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		375.5 375
58		{7-[2-(1-Benzyl-piperidin-4-yl)-ethyl]-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl}-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		470.7 470
59		{7-[2-(1H-Indol-3-yl)-ethyl]-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl}-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		412.6 412
60		(4-Methyl-7-phenyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl)-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		345.5 345
61		[7-(2,4-Dimethyl-phenyl)-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		373.5 373

69		Ethyl-(4-methyl-7-naphthalen-1-ylmethyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl)-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		437.6 437
70		Ethyl-[4-methyl-7-(tetrahydro-furan-2-ylmethyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		381.5 381
71		Ethyl-(4-methyl-7-thiophen-2-ylmethyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl)-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		393.6 393
72		(7-Benzo[1,3]dioxol-5-ylmethyl-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl)-ethyl-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		431.5 431
73		Ethyl-[4-methyl-7-(3-morpholin-4-yl-propyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		424.6 424
74		Ethyl-[4-methyl-7-(2-pyridin-2-yl-ethyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		402.6 402

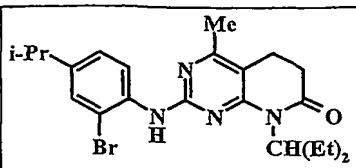
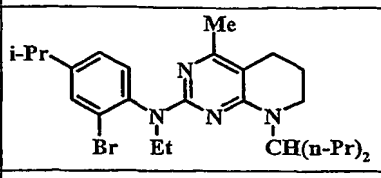
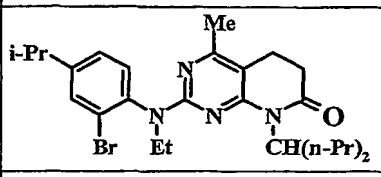
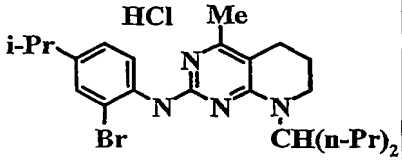
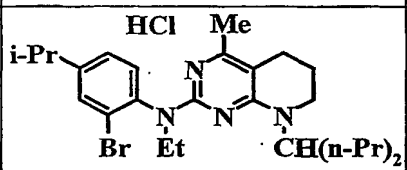
82		(7-Benzyl-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl)-ethyl-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		387.5 387
83		Ethyl-[7-(3-fluoro-benzyl)-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		405.5 405
84		[7-(3,4-Dimethoxy-benzyl)-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-ethyl-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		447.6 447
85		Ethyl-(4-methyl-7-phenethyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl)-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		401.6 401
86		(7-Allyl-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl)-ethyl-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		337.5 337
87		Ethyl-(4-methyl-7-propyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl)-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		339.5 339
88		Ethyl-(4-methyl-7-pentyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl)-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		367.6 367

96		[7-(1-Benzyl-pyrrolidin-3-yl)-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-ethyl-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		456.6 456
97		Ethyl-{7-[2-(3-fluoro-phenyl)-ethyl]-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl}-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		419.6 419
98		Ethyl-[4-methyl-7-(3-propoxy-propyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		397.6 397
99		[7-(2-[1,3]Dioxolan-2-yl-ethyl)-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-ethyl-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		397.5 397
100		Ethyl-[4-methyl-7-(5-methyl-pyrazin-2-ylmethyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		403.5 403
101		{7-[2-(1-Benzyl-piperidin-4-yl)-ethyl]-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl}-ethyl-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		498.7 498

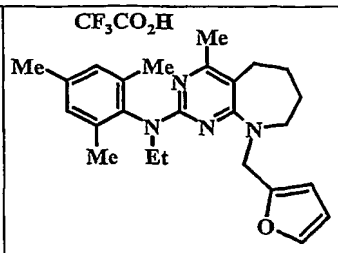
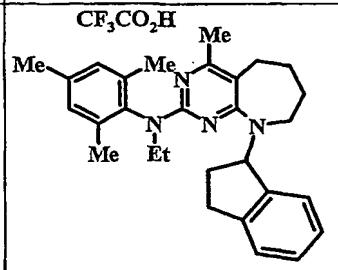
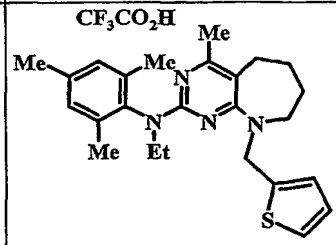
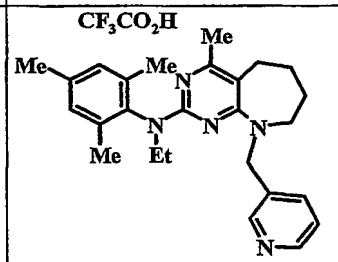
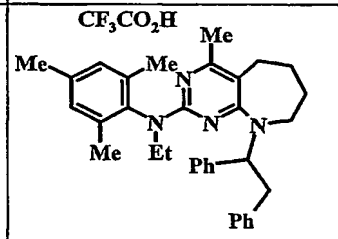
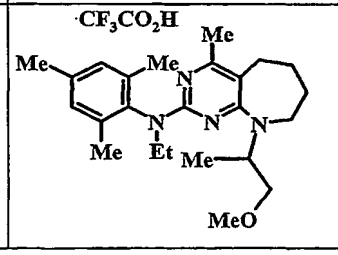
110		Benzyl-[4-methyl-7-(1-propyl-butyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		457.7 457
111		Cyclopropylmethyl-[4-methyl-7-(1-propyl-butyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		421.6 421
112		Allyl-[4-methyl-7-(1-propyl-butyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		407.6 407

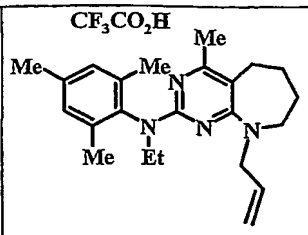
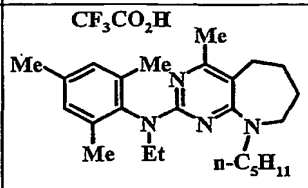
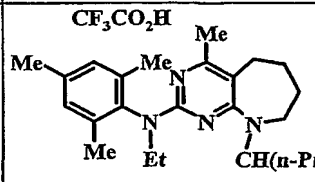
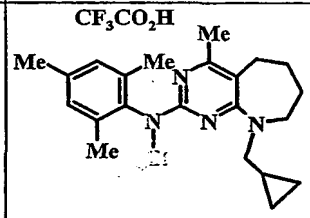
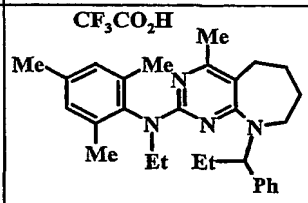
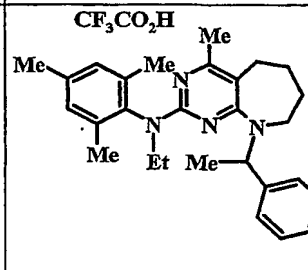
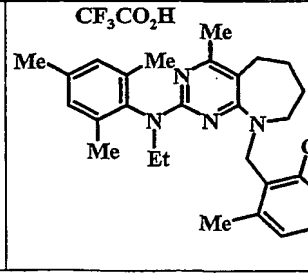
4-Methyl-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidines and 4-methyl-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-ones were prepared as shown in Scheme 2. In step (b) the Principal Synthesis was carried out with diethyl 2-acetylglutarate to incorporate a three-carbon carboxylic acid side chain at the 5-position of the pyrimidine XI. After conversion of the 6-hydroxy to a 6-chloro analogue with phosphorus oxychloride in step (c), condensation with a primary amine proceeds to afford a pyrimidone XIII.

In step (e) the lactam was reduction with BH_3-THF to afford the corresponding tertiary amine XIV. In addition to BH_3-THF, reduction of amides to amines can be carried out with lithium aluminum hydride diisobutylaluminum hydride or other hydride reducing agents. Sodium borohydride is less generally useful. Reductions with hydride reducing agents are usually run in aprotic solvents such as diethyl ether, THF and dimethoxyethane. Catalytic hydrogen also may be utilized for the reduction of amides but high temperature and pressure are typically required. (J. March, *supra* p.1212-13). In step (f) the amine is optionally substituted by alkylation as described previously.

115		2-(2-Bromo-4-isopropyl-phenylamino)-4-methyl-8-(1-propyl-butyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one	122-123	473.5 473
116		(2-Bromo-4-isopropyl-phenyl)-ethyl-[8-(1-ethyl-propyl)-4-methyl-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidin-2-yl]-amine		459.5 459
117		2-[(2-Bromo-4-isopropyl-phenyl)-ethyl-amino]-4-methyl-8-(1-propyl-butyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one	92-94	501.5 501
118		(2-Bromo-4-isopropyl-phenyl)-[4-methyl-8-(1-propyl-butyl)-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidin-2-yl]-amine; compound with hydrogen chloride	182-184	459.5 459
119		(2-Bromo-4-isopropyl-phenyl)-ethyl-[4-methyl-8-(1-propyl-butyl)-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidin-2-yl]-amine; compound with hydrogen chloride	201-205	487.5 487

The trifluoroacetic acid salt of ethyl-(4-methyl-9-thiophen-2-ylmethyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl)-(2,4,6-trimethyl-phenyl)-amine was prepared as shown in Scheme 3. In step (b) the Principal Synthesis was carried out with 3-acetyl-oxepan-2-one to incorporate a four-carbon side chain at the 5-position of the pyrimidine. Sequential conversion of the side chain and ring hydroxyls to the dichloride was carried out as described in Scheme 1. The cyclization step (d) and optional N-alkylation step (e) were carried out as described in Scheme 1.

121		Ethyl-(9-furan-2-ylmethyl-4-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl)-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		405.6 405
122		Ethyl-(9-indan-1-yl-4-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl)-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		441.6 441
123		Ethyl-(4-methyl-9-thiophen-2-ylmethyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl)-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		421.6 421
124		Ethyl-(4-methyl-9-pyridin-3-ylmethyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl)-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		416.6 416
125		[9-(1,2-Diphenyl-ethyl)-4-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl]-ethyl-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		505.7 505
126		Ethyl-[9-(2-methoxy-1-methyl-ethyl)-4-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl]-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		397.6 397

134		(9-Allyl-4-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl)-ethyl-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		365.5 365
135		Ethyl-(4-methyl-9-pentyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl)-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		395.6 395
136		Ethyl-[4-methyl-9-(1-propyl-butyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl]-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		423.7 423
137		(9-Cyclopropylmethyl-4-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl)-ethyl-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		379.6 379
138		Ethyl-[4-methyl-9-(1-phenyl-propyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl]-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		443.6 443
139		Ethyl-{9-[1-(4-fluoro-phenyl)-ethyl]-4-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl}-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		447.6 447
140		[9-(2,4-Dichloro-6-methyl-benzyl)-4-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl]-ethyl-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid		497.5 497

administration, among other routes of administration. The preferred manner of administration is generally oral using a convenient daily dosing regimen which can be adjusted according to the degree of affliction and the patient's response to the active ingredient.

A compound or compounds of the present invention, as well as their pharmaceutically useable salts, together with one or more conventional excipients, carriers, or diluents, may be placed into the form of pharmaceutical compositions and unit dosages. The pharmaceutical compositions and unit dosage forms may be comprised of conventional ingredients in conventional proportions, with or without additional active compounds or principles, and the unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. The pharmaceutical compositions may be employed as solids, such as tablets or filled capsules, semisolids, powders, sustained release formulations, or liquids such as solutions, suspensions, emulsions, elixirs, or filled capsules for oral use; or in the form of suppositories for rectal or vaginal administration; or in the form of sterile injectable solutions for parenteral use. A typical preparation will contain from about 5% to about 95% active compound or compounds (w/w). The term "preparation" or "dosage form" is intended to include both solid and liquid formulations of the active compound and one skilled in the art will appreciate that an active ingredient can exist in different preparations depending on the target organ or tissue and on the desired dose and pharmacokinetic parameters.

The term "excipient" as used herein refers to a compound that is useful in preparing a pharmaceutical composition, generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipients that are acceptable for veterinary use as well as human pharmaceutical use. The term "excipient" as used herein includes both one and more than one such excipient.

The phrase "pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid,

in aqueous propylene glycol solutions or may contain emulsifying agents such as lecithin, sorbitan monooleate, or acacia. Aqueous solutions can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing, and thickening agents. Aqueous suspensions can be prepared by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well known suspending agents.

The compounds of the present invention may be formulated for parenteral administration (*e.g.*, by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, for example solutions in aqueous polyethylene glycol. Examples of oily or nonaqueous carriers, diluents, solvents or vehicles include propylene glycol, polyethylene glycol, vegetable oils (*e.g.*, olive oil), and injectable organic esters (*e.g.*, ethyl oleate), and may contain formulatory agents such as preserving, wetting, emulsifying or suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution for constitution before use with a suitable vehicle, *e.g.*, sterile, pyrogen-free water.

The compounds of the present invention may be formulated for topical administration to the epidermis as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also containing one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents. Formulations suitable for topical administration in the mouth include lozenges comprising active agents in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

The compounds of the present invention may be formulated for administration as suppositories. A low melting wax, such as a mixture of fatty acid glycerides or cocoa butter is first melted and the active component is dispersed homogeneously, for example,

adhesive solid support. The compound of interest can also be combined with a penetration enhancer, e.g., Azone (1-dodecylaza-cycloheptan-2-one). Sustained release delivery systems are inserted subcutaneously into to the subdermal layer by surgery or injection. The subdermal implants encapsulate the compound in a lipid soluble membrane, e.g., silicone rubber, or a biodegradable polymer, e.g., polylactic acid.

Suitable formulations along with pharmaceutical carriers, diluents and excipients are described in *Remington: The Science and Practice of Pharmacy* 1995, edited by E. W. Martin, Mack Publishing Company, 19th edition, Easton, Pennsylvania. A skilled formulation scientist may modify the formulations within the teachings of the specification to provide numerous formulations for a particular route of administration without rendering the compositions of the present invention unstable or compromising their therapeutic activity.

The modification of the present compounds to render them more soluble in water or other vehicle, for example, may be easily accomplished by minor modifications (salt formulation, esterification, etc.), which are well within the ordinary skill in the art. It is also well within the ordinary skill of the art to modify the route of administration and dosage regimen of a particular compound in order to manage the pharmacokinetics of the present compounds for maximum beneficial effect in patients.

The term "therapeutically effective amount" as used herein means an amount required to reduce symptoms of the disease in an individual. The dose will be adjusted to the individual requirements in each particular case. That dosage can vary within wide limits depending upon numerous factors such as the severity of the disease to be treated, the age and general health condition of the patient, other medicaments with which the patient is being treated, the route and form of administration and the preferences and experience of the medical practitioner involved. For oral administration, a daily dosage of between about 0.01 and about 100 mg/kg body weight per day should be appropriate in monotherapy and/or in combination therapy. A preferred daily dosage is between about 0.1 and about 500 mg/kg body weight, more preferred 0.1 and about 100 mg/kg body weight and most preferred 1.0 and about 10 mg/kg body weight per day. Thus, for administration to a 70 kg person, the dosage range would be about 7 mg to 0.7 g per day. The daily dosage can be administered as a single dosage or in divided dosages, typically between 1 and 5 dosages per day. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect for the individual patient is

mL) and treated with cyanamid (5.0 g, 120 mmol). The resulting solution was heated to reflux for 43 hours and then concentrated under reduced pressure. The viscous residue so obtained was triturated with diethyl ether (2 x 100 mL) to afford the guanidine hydrochloride IV as an hygroscopic, light brown foam (22 g, 100%; ESIMS *m/z* (M+H) = 178).

step 2 - 5-(2-Hydroxy-ethyl)-2-(2,4,6-trimethyl-phenylamino)-pyrimidin-4-ol (V).

A solution of *N*-(2,4,6-trimethyl-phenyl)-guanidine hydrochloride (17 g, 80 mmol) in ethanol (100 mL) was treated with sodium methoxide (4.3 g, 80 mmol) in methanol (18 mL), followed by 3-acetyl-dihydro-furan-2-one (2-acetylbutyrolactone, 10.3 g, 80 mmol). The reaction mixture was heated to reflux for 19 hours and then concentrated under reduced pressure. The residue so obtained was suspended in water (200 mL), and the resulting mixture was adjusted to pH 5 by the careful addition of concentrated hydrochloric acid, saturated with sodium chloride, and extracted with chloroform (3 x 500 mL). The combined extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude orange syrup so obtained was chromatographed over silica gel, eluting with a gradient of 0 to 10% methanol in dichloromethane, to afford the pyrimidinol V as a white powder (7.5 g, 38%; ESIMS *m/z* (M+H) = 288).

step 3 - [4-Chloro-5-(2-chloro-ethyl)-pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine (VI).

To a vigorously stirred suspension of 5-(2-hydroxy-ethyl)-2-(2,4,6-trimethyl-phenylamino)-pyrimidin-4-ol (V; 4.6 g, 16 mmol) in toluene (100 mL) was added a solution of thionyl chloride (2.0 g, 17 mmol) in toluene (60 mL) over 30 minutes. The reaction mixture was stirred at room temperature for 69 hours and then concentrated under reduced pressure. The tan solid so obtained was dissolved in phosphorus oxychloride (49 g, 320 mmol) and heated to reflux for 19 hours. After cooling to room temperature, the reaction mixture was poured onto ice (500 g), neutralized with sodium hydrogen carbonate, and extracted with ethyl acetate (3 x 500 mL). The combined extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude brown solid was chromatographed over silica gel, eluting with a gradient of 10 to 30% ethyl acetate in hexane, to afford the chloropyrimidine VI as a pale yellow solid (3.8 g, 92%; ESIMS *m/z* (M+H) 324).

mixture was then concentrated under reduced pressure to afford 2-bromo-4-isopropyl-phenylamine; hydrochloride as a white solid (19.9 g, 100%), which was dissolved in warm ethanol (100 mL) and added to cyanamid (4.0 g, 95 mmol). The resulting solution was heated to reflux for 16 hours, with additional cyanamide (1.0 g, 24 mmol) being added after 4 h. The reaction mixture was then concentrated under reduced pressure, and the residue so obtained was triturated with diethyl ether (4 x 50 mL) to afford the guanidine hydrochloride as a tan semisolid (X; 21 g, 89%; ESIMS *m/z* (M+H) = 256).

step 2 - 3-[2-(2-Bromo-4-isopropyl-phenylamino)-4-hydroxy-6-methyl-pyrimidin-5-yl]-propionic acid ethyl ester (XI).

To a solution of *N*-(2-bromo-4-isopropyl-phenyl)-guanidine; hydrochloride (X; 21 g, 72 mmol) and 2-acetyl-pentanedioic acid diethyl ester (diethyl 2-acetylglutarate, 18 g, 79 mmol) in ethanol (100 mL) was added a solution of freshly prepared sodium ethoxide (87 mmol) in ethanol (50 mL). The reaction mixture was heated to reflux for 24 hours and then concentrated under reduced pressure. The residue so obtained was suspended in water (200 mL), and the resulting mixture was adjusted to pH 5 by the careful addition of concentrated hydrochloric acid, saturated with sodium chloride, and extracted with ethyl acetate (3 x 100 mL). The combined extracts were washed with brine (150 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude, brown oil so obtained was chromatographed over silica gel, eluting with a gradient of 0.5 to 6% methanol in dichloromethane, to afford the hydroxypyrimidine as a cream solid (XI; 7.2 g, 21%; ESIMS *m/z* (M+H) = 422).

step 3 - 3-[2-(2-Bromo-4-isopropyl-phenylamino)-4-chloro-6-methyl-pyrimidin-5-yl]-propionic acid ethyl ester (XII).

A solution of 3-[2-(2-bromo-4-isopropyl-phenylamino)-4-hydroxy-6-methyl-pyrimidin-5-yl]propionic acid ethyl ester (XI; 6.6 g, 16 mmol) in phosphorus oxychloride (14 g, 94 mmol) was heated to reflux for 2.5 hours. After cooling to room temperature, the reaction mixture was poured onto ice (150 g) and extracted with ethyl acetate (2 x 150 mL). The combined extracts were washed sequentially with brine (150 mL), saturated aqueous sodium bicarbonate (100 mL), and brine (100 mL), then dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude dark oil was chromatographed over silica gel, eluting with a gradient of 0 to 20% ethyl acetate in hexane, to afford the chloropyrimidine as a light yellow oil (XII; 3.8 g, 54%; ESIMS *m/z* (M+H) = 440).

isopropyl-phenyl)-[8-(1-ethyl-propyl)-4-methyl-5,6,7,8-tetrahydro-pyrido[2,3-*d*]pyrimidin-2-yl]-amine (XIV; 0.056 g, 0.13 mmol) in *N*,*N*-dimethylformamide (0.5 mL). After 30 minutes at room temperature, iodoethane (0.026 g, 0.17 mmol) was added, and the resulting mixture was stirred at room temperature for 14 hours. The reaction mixture was then poured onto water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined extracts were washed with brine (10 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The yellow oil so obtained was chromatographed over silica gel, eluting with a gradient of 20 to 50% ethyl acetate in hexane, to afford 116 as a pale yellow oil (0.040 g, 67%). ESIMS *m/z* 459 (M+H).

EXAMPLE 5

Ethyl-(4-methyl-9-thiophen-2-ylmethyl-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*]azepin-2-yl)-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid (123).

step 1 - 3-Acetyl-oxepan-2-one (XVII).

To a solution of diisopropylamine (2.2 g, 22 mmol) in tetrahydrofuran (100 mL) at -78 ^{0}C was added a solution of butyllithium in hexanes (1.6 M, 14 mL, 22 mmol), under nitrogen. The resulting solution was stirred at -78 ^{0}C for 45 min and then treated with oxepan-2-one (XVI, 2.3 g, 20 mmol) in tetrahydrofuran (50 mL) over 15 minutes. The resulting solution was stirred at -78 ^{0}C for 1 hour and then treated with pyruvonitrile (1.5 g, 22 mmol). The resulting solution was stirred at -78 ^{0}C for 10 minutes and then treated with water (0.4 mL). The mixture was then poured onto diethyl ether (400 mL) and water (400 mL). The water layer was further extracted with diethyl ether (450 mL). The combined extracts were washed with brine (50 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting yellow oil was chromatographed over silica gel, eluting with a gradient of 5 to 30% ethyl acetate in hexane, to afford the ketoester as a colorless solid (XVII; 1.5 g, 48%; mp 53-59 ^{0}C).

step 2 - 5-(4-Hydroxy-butyl)-6-methyl-2-(2,4,6-trimethyl-phenylamino)-pyrimidin-4-ol

A solution of *N*-(2,4,6-trimethyl-phenyl)-guanidine; hydrochloride (IV; 2.0 g, 9.4 mmol) in ethanol (10 mL) was treated with sodium methoxide (0.52 g, 9.5 mmol) in methanol (2.2 mL), followed by 3-acetyl-oxepan-2-one (1.3 g, 8.2 mmol) in ethanol (2 mL). The reaction mixture was heated to reflux for 21 hours and then concentrated under reduced pressure. The residue so obtained was suspended in water (200 mL), and the resulting

step 5 - Ethyl-(4-methyl-9-thiophen-2-ylmethyl-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*]azepin-2-yl)-(2,4,6-trimethyl-phenyl)-amine; compound with trifluoro-acetic acid (123).

(4-Methyl-9-thiophen-2-ylmethyl-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*]azepin-2-yl)-(2,4,6-trimethyl-phenyl)-amine (XX; 0.039 g, 0.10 mmol) was treated with a fine suspension of sodium hydride in *N*,*N*-dimethylformamide (0.18 M, 1.0 mL, 0.18 mmol) under nitrogen. After 1.25 hours shaking at room temperature, iodoethane (0.028 g, 0.18 mmol) in *N*,*N*-dimethylformamide (0.15 mL) was added, and the resulting mixture was shaken at room temperature for 8 hours, followed by 9 hours at 40 ^{0}C. The reaction mixture was then treated with trifluoroacetic acid (1 drop) and concentrated under reduced pressure. The residue so obtained was purified by preparative, reversed-phase HPLC, eluting with 0.1% trifluoroacetic acid/water/acetonitrile, to afford 123 (ESIMS *m/z* (M+H) = 421).

EXAMPLE 6

CRF Receptor Binding Assay

Human IMR-32 neuroblastoma cells are grown to 80% confluence in MEM medium containing 10% heat-inactivated FBS, 1mM sodium pyruvate, and 0.1mM nonessential amino acids. Cell membranes are prepared according the method of Dieterich and DeSouza (1996). The cells (~5E+9) are resuspended in 10 volumes of wash buffer (5 mM Tris HCl, 10 mM $MgCl_2$, 2 mM EGTA, pH 7.4 at RT), homogenized with a Polytron, and then centrifuged at 45,000 G for 20 min at 4°C. The membrane pellets are washed twice with wash buffer (45,000 G for 20 min at 4°C) and then resuspended (50 mM Tris HCl, 10 mM $MgCl_2$, 2 mM EGTA, pH 7.4 at RT). Protein concentration is determined using Pierce reagents and BSA as standard. Aliquots of 1-1.5 mL are stored at -80°C until binding assay.

The competition binding assay is performed in a final volume of 250 µl, which contains assay buffer (50 mM Tris-HCl, 10 mM $MgCl_2$, 2 mM EGTA, 0.2% BSA, 0.1mM bacitracin and 100 kIU/mL aprotinin pH 7.2 at R.T.), 0.05 nM [^{125}I]Tyr^0-ovine CRF (Du Pont New England Nuclear), 50 µg of membrane protein, and test compound at various concentrations. Non-specific binding is determined with 1 uM hCRF. Binding reactions are terminated after 2 hr incubation at 25°C by filtering through 96-w GF/C filter plate using a Packard Harvester (Filtermate 196). The 96-w filter plate is pre-treated with 0.3% polyethyleneimine and pre-washed with washing buffer (50 mM Tris-HCl, 10 mM $MgCl_2$, 2 mM EGTA, 0.2% BSA, pH 7.2 at 4°C). Unbound radioactivity is removed by four rapid washes (0.8 ml/well) with wash buffer. The radioactivity is quantified using a

Magnesium stearate	0.5%
Crosscarmellose sodium	2.0%
Lactose	76.5%
PVP (polyvinylpyrrolidine)	1.0%

The ingredients are combined and granulated using a solvent such as methanol. The formulation is then dried and formed into tablets (containing about 20 mg of active compound) with an appropriate tablet machine.

Composition for Oral Administration (C)

Ingredient	% wt./wt.
Active compound	1.0 g
Fumaric acid	0.5 g
Sodium chloride	2.0 g
Methyl paraben	0.15 g
Propyl paraben	0.05 g
Granulated sugar	25.5 g
Sorbitol (70% solution)	12.85 g
Veegum K (Vanderbilt Co.)	1.0 g
Flavoring	0.035 ml
Colorings	0.5 mg
Distilled water	q.s. to 100 ml

The ingredients are mixed to form a suspension for oral administration.

Parenteral Formulation (D)

Ingredient	% wt./wt.
Active ingredient	0.25 g
Sodium Chloride	qs to make isotonic
Water for injection to	100 ml

The active ingredient is dissolved in a portion of the water for injection. A sufficient quantity of sodium chloride is then added with stirring to make the solution isotonic. The solution is made up to weight with the remainder of the water for injection, filtered through a 0.2 micron membrane filter and packaged under sterile conditions.

The foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding. It will be obvious to one of skill in the art that changes and modifications may be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

All patents, patent applications and publications cited in this application are hereby incorporated by reference in their entirety for all purposes to the same extent as if each individual patent, patent application or publication were so individually denoted.

nitro, and -NR^aR^b, where R^a and R^b are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{1-6} alkylcarbonyl;

(*x*) 1,2-diphenylethyl,

(*xii*) C_{1-3} alkoxy-C_{1-6} alkyl, or,

(*xiii*) aryloxy-C_{1-6} alkyl said aryloxy group being optionally substituted with one to three substituents selected form the group consisting of C_{1-3} alkyl, C_{1-3} alkoxy and halogen;

R^2 is C_{1-6} alkyl or C_{1-3} haloalkyl;

R^3 is (*i*) hydrogen,

(*ii*) C_{1-6} alkyl optionally substituted with hydroxy, C_{1-3} alkoxy or C_{1-3} acyloxy,

(*iii*) C_{3-6} alkenyl,

(*iv*) C_{3-7} cycloalkyl,

(*v*) C_{3-7} cycloalkyl-C_{1-3} alkyl;

(*vi*) C_{3-7} cycloalkenyl,

(*vii*) C_{3-7} cycloalkenyl-C_{1-3} alkyl,

(*viii*) benzyl optionally substituted with one to three groups independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, aminosulfonyl, monoalkylaminosulfonyl, dialkylaminosulfonyl, halogen, haloalkyl, cyano, nitro, and -NR^aR^b, where R^a and R^b are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{1-6} alkylcarbonyl; and,

R^4 is aryl optionally substituted with one to three groups independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, aminosulfonyl, monoalkylaminosulfonyl, dialkylaminosulfonyl, halogen, haloalkyl, cyano, nitro, and -NR^aR^b, where R^a and R^b are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{1-6} alkylcarbonyl, and,

individual isomers, racemic or non-racemic mixtures of isomers, solvates, hydrates or pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 wherein

X^1 is $(CH_2)_n$ where n = 0 to 2;

R^1 is (*i*) C_{1-10} alkyl optionally substituted with a substituent selected from the group consisting of amino, C_{1-3} alkylamino, C_{1-3} dialkylamino, (C_{1-3} alkyl)arylamino and phenyl, said phenyl optionally substituted with *(a)* one to three substituents independently selected from the group consisting of C_{1-}

and R^b are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{1-6} alkylcarbonyl; and,

R^4 is aryl optionally substituted with one to three groups independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, aminosulfonyl, monoalkylaminosulfonyl, dialkylaminosulfonyl, halogen, haloalkyl, cyano, nitro, and $-NR^aR^b$, where R^a and R^b are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{1-6} alkylcarbonyl, and,

individual isomers, racemic or non-racemic mixtures of isomers, solvates, hydrates or pharmaceutically acceptable salts thereof

3. A compound according to claim 2 wherein

n is 0;

R^1 is (*i*) C_{1-10} branched or unbranched alkyl; or,

(*ii*) optionally substituted heteroaryl-C_{1-6}alkyl, said heteroaryl optionally substituted with a substituent selected from the group consisting of C_{1-3} alkyl, C_{1-3} alkoxy and halogen,

(*iii*) optionally substituted phenyl or heteroaryl said phenyl or heteroaryl optionally substituted with a substituent selected from the group consisting of C_{1-3} alkyl, C_{1-3} alkoxy and halogen;

(*iv*) C_{1-3} alkyl substituted with a phenyl said phenyl optionally substituted with a substituent selected from the group consisting of C_{1-3} alkyl, C_{1-3} alkoxy and halogen;

R^3 is (*i*) hydrogen,

(*ii*) C_{1-6} alkyl,

(*iii*) C_{3-7} cycloalkyl-C_{1-3} alkyl, or,

(*iv*) benzyl optionally substituted with C_{1-3} alkyl, C_{1-3} alkoxy or halogen;

R^4 is optionally substituted phenyl.

4. A compound according to claim 3 wherein R^1 is

(*i*) C_{1-10} branched or unbranched alkyl,

(*ii*) C_{1-10} alkyl substituted with a phenyl said phenyl optionally substituted, or

(*iii*) heteroaryl- C_{1-6} alkyl wherein said heteroaryl is2-thienyl, 2-furanyl or 3-indolinyl each of said heteroaryl optionally substituted.

5. A compound according to claim 4 wherein R^4 is 2,4-disubstituted- or 2,4,6-trisubstituted-phenyl.

Ethyl-[4-methyl-7-(2-pyridin-2-yl-ethyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine,

Ethyl-(4-methyl-7-pyridin-3-ylmethyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl)-(2,4,6-trimethyl-phenyl)-amine,

[7-(1-Benzyl-piperidin-4-yl)-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-ethyl-(2,4,6-trimethyl-phenyl)-amine,

Ethyl-[4-methyl-7-(2-piperidin-1-yl-ethyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine,

[7-(1,2-Diphenyl-ethyl)-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-ethyl-(2,4,6-trimethyl-phenyl)-amine,

Ethyl-(7-isopropyl-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl)-(2,4,6-trimethyl-phenyl)-amine,

Ethyl-[7-(2-methoxy-1-methyl-ethyl)-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine,

Ethyl-[4-methyl-7-(1-methyl-3-phenyl-propyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine,

(7-Benzyl-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl)-ethyl-(2,4,6-trimethyl-phenyl)-amine,

Ethyl-[7-(3-fluoro-benzyl)-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine,

[7-(3,4-Dimethoxy-benzyl)-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-ethyl-(2,4,6-trimethyl-phenyl)-amine,

Ethyl-(4-methyl-7-phenethyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl)-(2,4,6-trimethyl-phenyl)-amine,

(7-Allyl-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl)-ethyl-(2,4,6-trimethyl-phenyl)-amine,

Ethyl-(4-methyl-7-propyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl)-(2,4,6-trimethyl-phenyl)-amine,

[7-(2,4-Dimethyl-phenyl)-4-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-ethyl-(2,4,6-trimethyl-phenyl)-amine; as well as their acid addition salt with trifluoro-acetic acid.

8. A compound according to claim 5 wherein X^1 is $(CH_2)_n$, n is 0, R^1 is CH(n-propyl)$_2$, R^2 is CH_3, R^3 is CH_2CH_3 and R^4 is 2,4-disubstituted- or 2,4,6-trisubstituted-phenyl.

9. A compound according to claim 8, wherein the compound is selected from the group consisting of

Methyl-[4-methyl-7-(1-propyl-butyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine,

Ethyl-[4-methyl-7-(1-propyl-butyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine,

Isopropyl-[4-methyl-7-(1-propyl-butyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine,

Butyl-[4-methyl-7-(1-propyl-butyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine,

Cyclopentyl-[4-methyl-7-(1-propyl-butyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine,

Acetic acid 4-[[4-methyl-7-(1-propyl-butyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amino]-butyl ester,

Benzyl-[4-methyl-7-(1-propyl-butyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine,

Cyclopropylmethyl-[4-methyl-7-(1-propyl-butyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine, and

Allyl-[4-methyl-7-(1-propyl-butyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,4,6-trimethyl-phenyl)-amine; as well as their acid addition salt with trifluoro-acetic acid.

14. A compound according to claim 2 wherein

n is 2;

R^1 is (*i*) C_{1-10} branched or unbranched alkyl; or,

(*ii*) optionally substituted heteroaryl-C_{1-6}alkyl, said heteroaryl optionally substituted with a substituent selected from the group consisting of C_{1-3} alkyl, C_{1-3} alkoxy and halogen,

(*iii*) optionally substituted phenyl or heteroaryl said phenyl or heteroaryl optionally substituted with a substituent selected from the group consisting of C_{1-3} alkyl, C_{1-3} alkoxy and halogen;

(*iv*) C_{1-3} alkyl substituted with a phenyl said phenyl optionally substituted with a substituent selected from the group consisting of C_{1-3} alkyl, C_{1-3} alkoxy and halogen;

R^3 is (*i*) hydrogen,

(*ii*) C_{1-6} alkyl,

(*iii*) C_{3-7} cycloalkyl-C_{1-3} alkyl, or,

(*iv*) benzyl optionally substituted with C_{1-3} alkyl, C_{1-3} alkoxy or halogen;

R^4 is optionally substituted phenyl.

15. A compound according to claim 14 wherein R^4 is 2,4-disubstituted- or 2,4,6-trisubstituted-phenyl.

16. A compound according to claim 15 wherein X_1 is $(CH_2)_n$, n is 2, R^2 is CH_3, R^3 is CH_2CH_3 and R^4 is 2,4,6-trisubstituted-phenyl.

17. A compound according to claim 16, wherein the compound is selected from the group consisting of

(9-Cyclohexylmethyl-4-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl)-ethyl-(2,4,6-trimethyl-phenyl)-amine,

Ethyl-(9-furan-2-ylmethyl-4-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl)-(2,4,6-trimethyl-phenyl)-amine,

Ethyl-(9-indan-1-yl-4-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl)-(2,4,6-trimethyl-phenyl)-amine,

Ethyl-(4-methyl-9-thiophen-2-ylmethyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl)-(2,4,6-trimethyl-phenyl)-amine,

Ethyl-[4-methyl-9-(1-phenyl-propyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl]-(2,4,6-trimethyl-phenyl)-amine,

Ethyl-{9-[1-(4-fluoro-phenyl)-ethyl]-4-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl}-(2,4,6-trimethyl-phenyl)-amine,

[9-(2,4-Dichloro-6-methyl-benzyl)-4-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl]-ethyl-(2,4,6-trimethyl-phenyl)-amine,

Ethyl-[4-methyl-9-(2-phenoxy-ethyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl]-(2,4,6-trimethyl-phenyl)-amine,

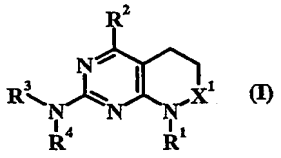
Ethyl-[4-methyl-9-(3-propoxy-propyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl]-(2,4,6-trimethyl-phenyl)-amine,

[9-(2,4-Dimethyl-phenyl)-4-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl]-ethyl-(2,4,6-trimethyl-phenyl)-amine,

[9-(2,4-Dimethyl-benzyl)-4-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl]-ethyl-(2,4,6-trimethyl-phenyl)-amine, and

(4-Methyl-9-[1]benzothiophen-2-ylmethyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-2-yl)-(2,4,6-trimethyl-phenyl)-amine; as well as their acid addition salt with trifluoro-acetic acid.

18. A process for the preparation of a compound according to formula I



(I)

wherein

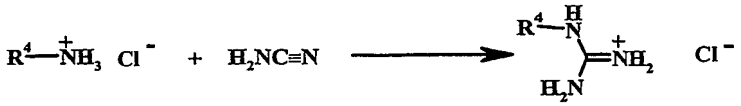
X^1 is $(CH_2)_n$ where n = 0 to 2;

R^1 is (*i*) C_{1-10} alkyl or C_{2-10} alkenyl optionally substituted with a substituent selected from the group consisting of hydroxy, cyano, amino, C_{1-3} alkylamino, C_{1-3} dialkylamino, (C_{1-3} alkyl)arylamino and phenyl, said phenyl optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, aminosulfonyl, monoalkylaminosulfonyl, dialkylaminosulfonyl, halogen, haloalkyl, cyano, nitro, and $-NR^aR^b$, where R^a and R^b are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{1-6} alkylcarbonyl,

dialkylaminosulfonyl, halogen, haloalkyl, cyano, nitro, and $-NR^aR^b$, where R^a and R^b are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{1-6} alkylcarbonyl; and,

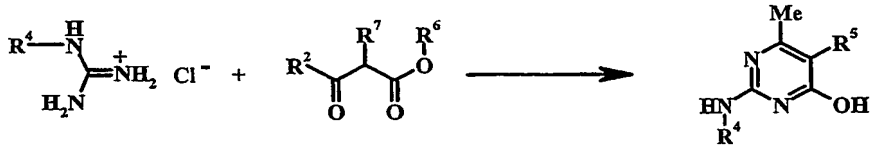
R^4 is aryl optionally substituted with one to three groups independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, aminosulfonyl, monoalkylaminosulfonyl, dialkylaminosulfonyl, halogen, haloalkyl, cyano, nitro, and $-NR^aR^b$, where R^a and R^b are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{1-6} alkylcarbonyl, and, individual isomers, racemic or non-racemic mixtures of isomers, solvates, hydrates or pharmaceutically acceptable salts thereof comprising the steps of:

(*i*) contacting an aryl amine hydrochloride XXII wherein R^4 is as defined above with cyanamide to afford an aryl guanidinium hydrochloride XXIII;



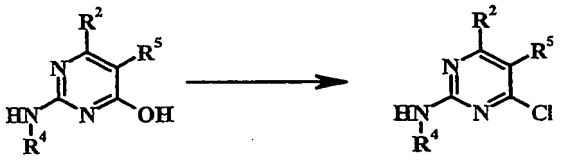
XXII XXIII

(*ii*) contacting said guanidine hydrochloride XXIII with a α-substituted β-keto ester XXIV wherein R^2 is C_{1-6} alkyl and R^6 is C_{1-6} alkyl and R^7 is alkoxycarbonylalkyl or R^6 and R^7 together are $(CH_2)_o$ and o is 2 to 4 in the presence of base to afford the pyrimidine XXV wherein R^5 is alkoxycarbonylalkyl or $(CH_2)_o$-OH;



XXIII XXIV XXV

(*iii*) contacting said pyrimidine with a chlorinating agent sufficiently reactive to convert XXV to the corresponding chloropyrimidine XXVI and to convert a hydroxyalkylene side chain present at R^5 to the corresponding chloroalkylene substituent;



XXV XXVI

(*iv*) contacting said chloropyrimidine XXVI with a primary amine under conditions which displace the chlorine atoms on the pyrimidine and the R^5 side chain when R^5 is hydroxyalkylene resulting in the formation of the fused heterocyclic ring

22. A medicament containing one or more compounds according to any one of claims 1 to 17 or 21 and pharmaceutically acceptable excipients for the treatment and prevention of CRF receptor mediated disorders.

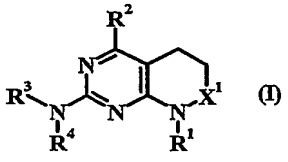
23. A medicament according to claim 22 for the treatment and prevention of phobias, stress-related illnesses, mood disorders, eating disorders, generalized anxiety disorders, stress-induced gastrointestinal dysfunctions, neurodegenerative diseases, and neuropsychiatric disorders .

24. A compound according to any one of claims 1 to 17 or 21 as well as its pharmaceutically acceptable salts thereof for use in the treatment or prevention of CRF receptor mediated disorders.

25. A compound according to claim 24 for the treatment and prevention of phobias, stress-related illnesses, mood disorders, eating disorders, generalized anxiety disorders, stress-induced gastrointestinal dysfunctions, neurodegenerative diseases, and neuropsychiatric disorders .

26. The use of a compound according to claim 1 to 17 or according to claim 21 in the manufacture of a medicament for the treatment or prevention of CRF receptor mediated disorders.

27. The use of a compound of formula I:



(I)

wherein

X^1 is C=O;

R^1 is (*i*) C_{1-10} alkyl or C_{2-10} alkenyl optionally substituted with a substituent selected from the group consisting of hydroxy, cyano, amino, C_{1-3} alkylamino, C_{1-3} dialkylamino, (C_{1-3} alkyl)arylamino and phenyl, said phenyl optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, aminosulfonyl, monoalkylaminosulfonyl, dialkylaminosulfonyl, halogen,

(*viii*) benzyl optionally substituted with one to three groups independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, aminosulfonyl, monoalkylaminosulfonyl, dialkylaminosulfonyl, halogen, haloalkyl, cyano, nitro, and $-NR^aR^b$, where R^a and R^b are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{1-6} alkylcarbonyl; and,

R^4 is aryl optionally substituted with one to three groups independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, aminosulfonyl, monoalkylaminosulfonyl, dialkylaminosulfonyl, halogen, haloalkyl, cyano, nitro, and $-NR^aR^b$, where R^a and R^b are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{1-6} alkylcarbonyl, and,

individual isomers, racemic or non-racemic mixtures of isomers, solvates, hydrates or pharmaceutically acceptable salts thereof in the manufacture of a medicament for the treatment or prevention of CRF receptor mediated disorders.

28. The use of claim 27 wherein the compound is selected from the group consisting of

2-(2-Bromo-4-isopropyl-phenylamino)-8-(1-ethyl-propyl)-4-methyl-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one,

2-(2-Bromo-4-isopropyl-phenylamino)-4-methyl-8-(1-propyl-butyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one,

2-[(2-Bromo-4-isopropyl-phenyl)-ethyl-amino]-4-methyl-8-(1-propyl-butyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one, as well as their salt with hydrochloric acid.

29. The use of any one of claims 26 to 28, wherein the disease state is selected from the group consisting of phobias, stress-related illnesses, mood disorders, eating disorders, generalized anxiety disorders, stress-induced gastrointestinal dysfunctions, neurodegenerative diseases, and neuropsychiatric disorders.

30. The compounds formulation, processes, methods and uses substantially as described herein.

International application No.
PCT/EP2004/004411

INTERNATIONAL SEARCH REPORT

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 21 corresponds to a product-by-process claim which is not allowable here since the protection for the mentioned compounds can be obtained by a "normal" wording according to claim 1. Present claim 30 refers to embodiment according to the description which is not allowable.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.